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### **REMARKS/ARGUMENTS**

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Non-elected claims 1, 2, 11-21 and 23-25 have been cancelled without prejudice to the filing of a divisional application covering same. Claim 22 has also been cancelled without prejudice.

On page 11 of the Action, the Examiner rejects claims 5-10 under 35 USC 112, second paragraph, as allegedly being indefinite. This rejection is addressed first since the response provided has relevance to the art-based rejections which are considered in turn below.

Claim 5 is drawn to a method of enhancing the ability of a cell to degrade a particle. The method comprises introducing into the cell a nucleic acid sequence encoding an Fc receptor comprising an L-T-L sequence in a cytoplasmic domain thereof. The claim requires that the Fc receptor comprise a  $\gamma$  chain cytoplasmic domain modified to comprise at least one L-T-L peptide.

In rejecting the claims as indefinite, the Examiner questions "why said cytoplasmic domain would have to be modified since it inherently possesses one L-T-L motif". In fact, the required  $\gamma$  chain cytoplasmic domain does not inherently possess an L-T-L motif. It possesses an L-T-L motif only if modified to do so, as in the case of the instant invention.

To illustrate this point, Applicants submit herewith a schematic diagram of human Fc receptors from Paul's "Fundamental Immunology" textbook. It will be clear from the diagram that Fc $\gamma$ RII does not contain a  $\gamma$  chain whereas Fc $\gamma$ RI, Fc $\gamma$ RIIIA, Fc $\epsilon$ RI and Fc $\alpha$ R do contain  $\gamma$  chains.<sup>1</sup>

The present invention results, at least in part, from Applicants' demonstrations that the L-T-L motif in the cytoplasmic domain of Fc $\gamma$ RIIA mediates lysosome fusion and that Fc $\gamma$ RIIA-mediated phagocytosis and lysosomal trafficking are composed of two distinct steps mediated by individual signaling motifs.

Applicants conducted studies with a receptor that does not contain an L-T-L motif. That is, the  $\gamma$  chain of various Fc receptors, such as Fc $\gamma$ RI and Fc $\gamma$ RIIIA, was utilized. Upon mutation of the  $\gamma$  chain to contain an L-T-L motif, targeting internalized particles to lysosomes was significantly enhanced (see Figure 5 of the subject application). This study demonstrates that lysosome targeting ability can be transferred to other receptors by translocating the L-T-L motif.

The Examiner is urged to reconsider claim 5 in view of the above clarifying comments. It is believed that having done so, the Examiner will find withdrawal of the rejection to be in order.

Claims 5-10 and 22 stand rejected as allegedly representing obviousness-type double patenting over claims 1-9, 14, 15 and 17 of USP 5,776,910 in view of Downey et

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<sup>1</sup> The Examiner is urged to note the comment at the top of the right column of page 66 of the Paul text provided regarding the confusion surrounding the nomenclature (particularly as it relates to the use of " $\gamma$ ").

al. Withdrawal of the rejection is submitted to be in order in view of the cancellation of claim 22 and comments that follow.

Claim 5 requires an Fc receptor comprising a  $\gamma$  chain cytoplasmic domain modified to include at least one L-T-L.

The claims of the cited patent make no mention of an L-T-L sequence, and nothing in the cited patent claims teaches or would have been suggestive of L-T-L sequences in the environments of the instant claims. The teachings of Downey et al in no way alter this fact.

The Examiner comments that the L-T-L motif is normally present in the cytoplasmic domain of Fc $\gamma$ RIIA. The instant claims, however, require a  $\gamma$  chain cytoplasmic domain not present in Fc $\gamma$ RIIA and, as indicated above, the  $\gamma$  chain does not naturally include any L-T-L motif. Accordingly, withdrawal of the rejection is clearly in order and same is requested.

Claims 5-10 and 22 stand rejected as allegedly representing obviousness-type double patenting over claims 1-9, 14, 15 and 17 of USP 6,068,983 in view of Downey et al. Withdrawal of the rejection is in order in view of the cancellation of claim 22 and for the reasons that follow.

Again, claim 5 requires an Fc receptor comprising a  $\gamma$  chain cytoplasmic domain modified to include at least one L-T-L.

The claims of the cited patent make no mention of an L-T-L sequence, and nothing in the cited patent claims teaches or would have been suggestive of L-T-L

sequences in the environments of the instant claims. The teachings of Downey et al in no way alter this fact.

The Examiner again comments that the L-T-L motif is normally present in the cytoplasmic domain of FcγRIIA. The Examiner is again reminded that the instant claims require a γ chain cytoplasmic domain not present in FcγRIIA. As indicated above, the γ chain does not naturally include any L-T-L motif. Accordingly, withdrawal of the rejection is requested.

Claims 5 and 7-10 stand rejected under 35 USC 102(b) as allegedly being anticipated by Downey et al. The rejection is traversed.

As the Examiner notes, Downey et al relates to FcγRIIA. Downey et al neither teaches, nor would it have suggested, modified receptors of the type recited in claim 5. That is, Downey et al does not teach modifying a γ chain cytoplasmic domain (which does not naturally include a L-T-L motif) to include an L-T-L motif. Accordingly, reconsideration is requested.

Claims 5-8 and 10 stand rejected under 35 USC 102(b) as allegedly being anticipated by Schreiber et al ('910). The rejection is traversed.

Schreiber et al is silent as regards an L-T-L sequence and in no way teaches, inherently or explicitly, modified receptors of the type recited in the instant claims. That is, Schreiber et al does not teach modifying a γ chain cytoplasmic domain so as to include an L-T-L motif. Accordingly, reconsideration is requested.

SCHREIBER et al  
Appl. No. 09/989,298  
July 27, 2004

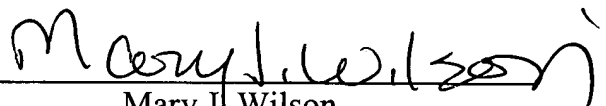
Claims 5-8 and 10 stand rejected under 35 USC 102(e) as allegedly being anticipated by Schreiber et al ('983). The rejection is traversed.

The reference says nothing of L-T-L sequences and cannot be viewed as teaching modification of a  $\gamma$  chain cytoplasmic domain so as to include an L-T-L motif as required by the instant claims. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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# FUNDAMENTAL IMMUNOLOGY

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*FOURTH EDITION*

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Editor

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Printer: Courier-Westford

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Printed in the United States of America

9 8 7 6 5 4 3 2 1

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**Library of Congress Cataloging-in-Publication Data**

Fundamental immunology / editor, William E. Paul. — 4th ed.

p. cm.

Includes bibliographical references and index

ISBN 0-7817-1412-5

1. Immunology. I. Paul, William E.

[DNLM: 1. Immunity. QW 540 F981 1998]

QR181.F84 1998

616.079—dc21

DNLM/DLC

for Library of Congress

98-3611

CIP

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Three large classes of molecules can bind Fc regions: glycosyltransferases, which recognize oligosaccharide derivatives on antibodies, lectin-like molecules, and receptors belonging to the IgSF. Of the "true" FcR that recognize antibody protein determinants rather than carbohydrate, all FcR thus far identified belong to the IgSF, other than the low-affinity IgE receptor (CD23/FcεRII). These molecules include FcγR I, II, and III (CD64, CD32, and CD16), FcεRI, FcαR (CD89), and the pIgR, which has already been discussed. All cells of lymphoid origin express FcRs, although the profiles and isotype specificities between lineages can vary greatly (reviewed in refs. 190 and 191). While receptors for all classes of immunoglobulin have been described as biological activities, human FcμR and FcδR have not yet been cloned. Thus far, the FcγR proteins and FcεRI are the most well characterized examples of these molecules.

### FcγR Molecules

Receptors for the Fc portion of IgG are of three types (reviewed in ref. 192). FcγRI (CD64) is a high-affinity receptor and the only one able to bind monomeric IgG. It possesses three extracellular Ig-like domains. FcγRII (CD32) and FcγRIII (CD16) are both low-affinity receptors that bind IgG-containing immune complexes. They each have only two extracellular Ig homology domains. Schematic diagrams of the FcγRI, FcγRII, FcγRIII complexes, along with the FcεRI and FcαR complexes, are presented in Fig. 22.

FcγRI is a 70-kD glycoprotein that is constitutively expressed at low levels on monocytes and macrophages. IFN-γ upregulates its levels on these cells, and also can induce its expression by neutrophils. FcγRI's affinity for IgG is highest for the IgG1 and IgG3 subclasses ( $K_D = 10^{-8}$  M), tenfold lower for IgG4, and will not bind IgG2. Functionally, the primary effect of cross-linking FcγRI molecules appears to be the potentiation of both ADCC and phagocytosis. As IFN-γ enhances both of these activities by the cell types known to express FcγRI, this would fit well with their being important roles for the receptor.

Like surface immunoglobulin, FcγRI requires accessory proteins in order to transmit signals. This is, in fact, a common feature of most FcRs (except for FcγRII) and an interesting parallel between the IgSF antigen receptors (BCR and TCR) and the IgSF "indirect"

antigen receptors (the FcR), which use antibody to bridge the span between FcR and antigen (193). In the specific case of FcγRI, the actual signaling molecule is a 12γ-kD transmembrane protein designated the "γ-subunit" or, more generally, FcγR. This nomenclature can be particularly confusing, as the "γ" of FcγR refers not to the fact that it is part of the of FcγR complex (the receptor for γ-class immunoglobulin), but rather to γ as an individual subunit of a multi-molecule complex. In any case, for the FcγRI complex, the α subunit is the actual IgSF protein FcγRI, and the γ subunit is FcγR, which forms a disulfide-linked homodimer. Complicating terminology further, FcγR is also a subunit of other FcR complexes, including that of the FcγRIIIA and those of the non-FcγR, FcεRI and FcαR. Intriguingly, FcγR is a close homologue of the TCR-associated protein CD3ζ. In fact, CD3ζ cannot only heterodimerize with FcγR, but also has been shown to be capable of functionally substituting for FcγR as the signal-transducing subunit of the FcγRIIIA receptor complex (194).

The situation for FcγRII (CD32) is even more complex. FcγRII is the product of three distinct but homologous genes: FcγRIIA, FcγRIIB, and FcγRIIC. This is further complicated by the fact that at least two of the FcγRII genes are alternatively spliced to generate multiple isoforms (195). The FcγRIIA gene gives rise to two transcripts: FcγRIIa1, which has a transmembrane domain, and FcγRIIa2, which lacks it. The FcγRIIB gene has three isoforms—FcγRIIb1, FcγRIIb2, and FcγRIIb3—generated by differential splicing and alternative polyadenylation processing. Collectively, the FcγRII variants are the most ubiquitously expressed FcγRs, being present on monocytes, macrophages, neutrophils, B lymphocytes, megakaryocytes, and platelets. Specifically, megakaryocytes express FcγRIIA (both isoforms), B lymphocytes express FcγRIIB (b1 and b2 transcripts) and FcγRIIC, and cells of myelomonocyte derivation produce at least one or more isoforms from all three genes (195).

Functionally, due to their expression on many cell types, FcγRII signals cause diverse effects. When cell surface FcγRII engage IgG immune complexes (all subclasses, with varying affinities), they potentiate several biologic changes, most immunoregulatory in nature. Generally, these signals down modulate IgG-, IgA-, and IgE-mediated activations of a number of cell types, including monocytes and macrophages, granulocytes, mast cells, and Langerhans and other dendritic cells. They also induce platelet aggregation at the site of immune complexes and effect B cell feedback inhibition by down-

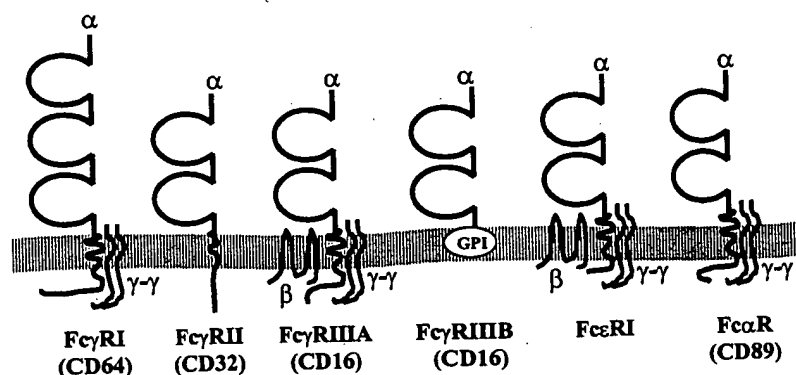


FIG. 22. Schematic diagram of human immunoglobulin Fc receptors belonging to the IgSF. Each Ig domain is depicted as a rounded bulge. The α chains are the components of the receptor complex that determine binding specificity. β and γ chains are responsible for association and signal propagation by the receptor(s).